

**Center for Scientific Review
Center for Scientific Review Advisory Council Meeting
National Institutes of Health
U.S. Department of Health and Human Services**

September 26, 2016

The Center for Scientific Review Advisory Council (CSRAC) convened at 8:30 a.m., Monday, September 26, 2016, at the Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, MD. The entire meeting was held in open session. Richard Nakamura, Ph.D., presided as chair.

Members Present

Roberta Diaz Brinton, Ph.D. (video)
Susan Essock, Ph.D.
Michael Hollingsworth, Ph.D.
Richard Nakamura, Ph.D.

Harry Orr, Ph.D.
Mary Sano, Ph.D. (special guest)
Stephan Targan, M.D.
Jennifer West, Ph.D.

Rene Etcheberrigaray, M.D., was the executive secretary for the meeting.

I. Welcome, Introduction, and Overview

Dr. Nakamura, CSR Director, welcomed CSRAC members, staff, and other attendees. He asked CSRAC members to introduce themselves and thanked them for their service. He highlighted recent appointments across NIH and within CSR. He then asked for a motion to approve the minutes from CSRAC's March 14, 2016, meeting. CSRAC approved the minutes.

II. NIH Key Issues in FY 2017

Lawrence A. Tabak, D.D.S., Ph.D., NIH Principal Deputy Director, focused on three topics: budget update for fiscal year (FY) 2017, priority issues related to the Presidential transition and to rigor and reproducibility, and a follow-up on the NIH strategic plan.

Budget Update

The NIH program level has improved in nominal dollars since 1998, but not in the purchasing power of those funds. The FY2017 budget requests an \$825 million increase. Applicant success rate would decrease slightly, because a significant percentage of that increase was requested for the National Cancer Moonshot, Precision Medicine Initiative, and Brain Initiative. The next administration will submit the FY2018 budget.

Priority Issues

Presidential Transition

NIH has only two political appointments: NIH Director, which requires Senate confirmation, and Director of the National Cancer Institute, which does not. This situation provides stability going from one administration to the next. The Partnership for Public Service has created the Center for Presidential Transition to try to harmonize an approach. Two councils convened by the Obama Administration are coordinating transition issues, and both campaigns have access to office

space. Although the process should result in a quicker start than in the past, it is a time of uncertainty.

Rigor and Reproducibility

Four deficiencies in experimental procedures have led to problems in rigor and reproducibility:

- ***Insufficient reporting in publications:*** Most pre-clinical studies do not report their methodological approaches, such as the sample size and exclusion criteria.
- ***Small, underpowered studies:*** Many animal studies have very small sample sizes, which means the effect may not hold up when replicated. A conundrum arises because of pressure to use the fewest number of animals possible, as well as funding limitations.
- ***P-hacking:*** Some researchers reanalyze data sets, either willingly or from lack of statistical understanding, to make non-significant results appear significant.
- ***Concern about the researcher's degrees of freedom:*** Making posthoc decisions about a number of variables (e.g., how to combine data, which data points to exclude) can lead to false positives, suggesting a more rigid approach may increase rigor and reproducibility. However, some express concern that a focus on procedures hampers creativity.

NIH efforts to address the underlying issues include the following:

- ***Raise community awareness:*** Over 135 journals have endorsed a set of principles related to reporting, and other organizations also have taken up the challenge;
- ***Enhance training:*** NIH is continuing to develop modules and workshops to train intramural and extramural researchers on how to enhance reproducibility;
- ***Adopt a more systematic review process:*** New grant guidelines, including reviewer guidance, cover how to present research strategy in an application;
- ***Share information and data:*** PubMed Commons allows researchers to share opinions on publications indexed by PubMed. Other efforts include preprint servers;
- ***Increase stability for investigators:*** Longer grants with more stable support, now pursued in several Institutes and Centers (ICs), can remove the pressure to show short-term results.

Dr. Tabak suggested individual scientists can play a role by stimulating discussion, increasing transparency, promoting training in experimental design, encouraging data and material sharing, and considering submission of refutations where needed.

NIH-Wide Strategic Plan

The plan, released in 2015, called for transparency for funding thresholds. These thresholds are now available across the spectrum of R01 grants, and will be available by IC in early 2017.

Discussion Highlights

- ***Research strategies:*** Related to reproducibility, Roberta Diaz Brinton, Ph.D., noted that one successful strategy would be to collaborate with statisticians to design animal studies like clinical trials. She suggested NIH develop an “app” to support power analyses for animal studies.
- ***Guidance on rigor and reproducibility:*** Michael Hollingsworth, Ph.D., noted a lack of knowledge in the scientific community about how to address research strategy in grant applications. Dr. Nakamura explained some of the guidance given to reviewers.

III. Scoring of Applications in Half Point Increments after Discussion: Pilot Study

Amy Rubinstein, Ph.D., Scientific Review Officer (SRO), noted the pilot study she coordinated addresses a critical question about how best to score applications. Because final scoring of the best applications is often limited to two or three whole point choices, score compression and tied scores can make funding decisions challenging.

In the study, after final voting of each application, reviewers were invited to provide a second score that could range from a half point better to a half point worse than the official score. Alternate scores were tabulated and compared with official scores. They were not shared with the applicants or program officers (POs).

Dr. Rubinstein reviewed the results of scoring 1,371 applications reviewed in over 30 study sections related to changes in average scores, distribution of scores, and scoring compression. The results varied by study section, but about one-half reduced scoring compression. About two-thirds of reviewers liked the opportunity to provide half point scores, and a minority did not.

Discussion Highlights

- **Preliminary versus final scores:** In response to a question from Stephan Targan, M.D., Dr. Nakamura said final scores were used to see the effect of half points on peaks in scoring.
- **PO Reaction:** In response to a question from Dr. Hollingsworth, Dr. Rubinstein said the half-point system received informal PO support, but no formal survey has taken place.
- **Reaction by reviewers:** Jennifer West, Ph.D., asked if the gradients changed the order. Dr. Rubinstein noted a few study sections did direct ranking, and they would look at the data.
- **Next steps:** Dr. Nakamura asked CSRAC whether to offer this as a trial under real conditions or continue with refinements. Dr. Targan suggested first looking at direct ranking more closely. Mary Sano, Ph.D., questioned the effect if reviewers had to announce the score as out of range. Harry Orr, Ph.D., said the scoring system was generally a good idea, but peaks would still occur.

IV. Alzheimer's Research Initiatives: The Critical Importance of Review

Richard Hodes, M.D., Director of the National Institute on Aging (NIA), thanked CSR for its role in reviewing increased applications stemming from the National Alzheimer's Project Act.

National Plan to Address Alzheimer's Disease

A national plan, released in 2012 and updated annually, calls for funding for research, care, and services. It includes 86 research implementation milestones. The NIA has received significantly increased funding to implement the plan. The legislation also requires NIH to annually submit directly to Congress a report about what is needed in terms of research funding for the disease.

Management

NIA received a \$350 million increase in its appropriation for FY 2016. Before knowing the details about the budget increase, but anticipating the possibility, NIA released 10 program announcements (PARs) on areas of Alzheimer's disease and related dementias research. CSR was essential in managing the review, particularly so two submission deadlines could occur in

FY 2016. Through outreach, more small business applications were also submitted, an area that NIA has considered underdeveloped.

Future Challenges

The cumulative number of initiatives will grow to more than 40 in FY 2017, including 27 new concepts to be reviewed by the NIA Council. All are connected to the research implementation milestones in the national plan and reflect planning for actual and potential funding increases. Accommodating them shows the critical role of review.

Discussion Highlights

- **CSR involvement:** Dr. Nakamura noted the appropriations included funds for expanded review, including CSR personnel. CSR managed the reviews of the PARs, while NIA managed the reviews for its request for applications (RFA). In answer to a question from Dr. Brinton, Dr. Nakamura said CSR has been able to ensure the necessary reviewer expertise.

V. Clinical Trials Research and Other Authority

Kathy Hudson, Ph.D., Deputy Director of Science, Outreach, and Policy, discussed how NIH is working to improve the transparency of clinical trials it supports. These trials represent about 10 percent of the NIH budget. She explained federal requirements to register clinical trials at clinicaltrials.gov and to post aggregate results. Sharing data provides benefits to the public, researchers, and current and potential subjects.

Final Rule and NIH Policy for Clinical Trials

Effective January 17, 2017, with compliance expected 90 days later, a final rule related to clinical trials takes effect. It specifies reporting and registration requirements, expands the scope of trials covered, requires additional registration and summary results information, provides a checklist for evaluating which clinical trials are covered and who is responsible, and requires additional types of adverse event information. It includes enforcement mechanisms.

The NIH policy expands to all phases of a trial. It does not apply to clinical trials using NIH-supported infrastructure but not directly NIH-supported, nor trials initiated before the effective date. The NIH-FDA Leadership Council developed a template to achieve consistency.

Additional policies include:

- **Single Institutional Review Board (sIRB):** Another recent NIH policy covers use of an sIRB for all domestic sites of multi-site studies. NIH has published guidance on the use of direct and indirect costs and is developing implementation guidance and outreach resources.
- **Clinical Trial Funding Opportunity Announcement (FOA):** All applications that include a clinical trial must be submitted through a clinical-trial FOA. The Office of Extramural Research is finalizing a template, and ICs will have flexibility in how they develop FOAs.

Precision Medicine Initiative Cohort

Through the Precision Medicine Initiative (PMI), the All of Us research program, 1 million or more volunteers are being recruited to create a longitudinal cohort. The cohort will provide many scientific opportunities as the largest such cohort in the United States. Partnerships with federally

qualified health centers, the Veterans Administration, and academic medical centers are building a diverse and inclusive cohort.

Discussion Highlights

- ***PMI cohort samples:*** In answer to a question from Dr. Hollingsworth, Dr. Hudson explained the data and samples being collected. The study is creating a small, high-value dataset that will expand over time. A subcommittee to the Advisory Council to the Director has held workshops on PMI's scientific opportunities. Data will live in the cloud where researchers can access it.
- ***Reporting:*** Dr. Hollingsworth asked whether new reporting rules will discourage researchers from doing clinical trials. Dr. Hudson noted the rule asks investigators to think up front about their outcome measures and analysis, which they should already do. Also, clinicaltrials.gov requires data submission in the absence of publications.

VI. Internet Assisted Meeting Review 2016

Robert Freund, Ph.D., Chief of the AIDS and Related Research Integrated Review Group (IRG), presented an overview of the Internet Assisted Meeting (IAM) format.

Improvements and Usage, 2006–2016

IAM provides a threaded discussion. Improvements over the years include increased server capacity, the ability to cluster applications, and other technical advances. About 5 percent of CSR applications are reviewed through IAM, and about one-third of SROs use it for one or more meetings a year—usually for smaller meetings. Most (60 percent) IAM meetings involve 15 or fewer applications, but 20 percent have involved more than 30 applications.

IAM Survey

CSR surveyed reviewers, POs, and SROs on IAM. Questionnaires had three topic clusters: logistics, user experience, and quality of review. Dr. Freund focused on the quality of review cluster, which had five seven-point Linkert-type statements and two multiple-choice questions.

SROs had the most favorable response about the quality of review, reviewers were somewhat less favorable than SROs, and only 36 percent of POs said an IAM discussion was thorough. One of the key questions was whether reviewers would be comfortable having their own application reviewed using the IAM format. When reviewers were asked about their comfort level if their own application were considered through IAM, using a 7-point Likert-type scale. Forty-seven percent either agreed or strongly agreed and 22 percent either disagreed or strongly disagreed.

Survey Conclusions and Lessons

Comparing formats, reviewers felt face-to-face meetings provided the highest quality (84 percent favorable), followed by telephone-assisted meetings (76 percent), video assisted meetings (70 percent), and IAM (68 percent).

The survey pointed out some technical and perception issues, but most importantly underscored that reviewer engagement is key for quality review. Some steps to maximize IAM engagement

include synchronous attendance, semi-synchronous discussion, visibility of reviewers' online status to all panel members, and active SRO and chair involvement.

Discussion Highlights

- **Comfort with IAM:** In response to a comment by Dr. Sano, Dr. Freund agreed comfort level with the technology would keep reviewers more engaged.
- **SRO response:** Dr. Hollingsworth noted relatively higher marks from SROs may reflect the SROs who have chosen to use it. He asked about any analysis on IAM and percentiling of similar grants. Dr. Freund said no obvious difference in scoring patterns has been detected.
- **Hybrid approach:** Dr. Brinton suggested combining IAM with other formats. From the audience, Wei-Qin Zhao, Ph.D., noted some panels use IAM for the first stage of applications, then move to telephone or face to face.
- **Reviewer engagement:** Dr. Orr suggested the length of time that a format is in use may contribute to reviewer preferences. Dr. Zhao said the fact that IAM may have less timely responses may contribute to a preference for telephone reviews.

VII. CSR Update and Discussion

The CSR update began with a presentation by Lee Mann, Ph.D., J.D., SRO and Anonymization Project Coordinator, on an upcoming anonymization experiment. Dr. Nakamura then discussed other CSR issues.

Program Evaluation of NIH Peer Review Processes: The Role of Anonymization

Dr. Mann discussed an upcoming experiment to learn if factors such as race and bias influence peer review.

The primary aim of the study is to determine if masking personally identifiable information (PII) from grant applications reduces the differences in final scores between black and white applicants. Secondary aims are to look at any differences related to sex, established versus early investigators, and more- versus less-research intensive institutions.

Research Design

Twelve hundred previously reviewed applications from 2014–2015 will be anonymized, with information about the applicant and institution redacted. They include 800 applications (400 black, 400 white) matched by science area, degree, and other aspects, and 400 randomly selected applications from white applicants. Reviewers will provide preliminary scores and written critiques. They will also be asked if they could identify the investigator, institution, grantsmanship, and other information. CSR expects to award a contract at the end of September for a two-year study.

Discussion on Anonymization Experiment

- **Selection of reviewers:** In answer to a question from Dr. Hollingsworth, Dr. Mann said SROs provided reviewer rosters, from which participating reviewers can be selected.
- **Applications selected:** Dr. Mann stressed this is a first study and will not reflect real-world conditions. The initial focus is on African Americans. The paired matching of applications will be made based on science area.

- ***Vetting the study:*** Dr. Essock expressed her support for the aims of the study but urged CSR to vet the methods used by the contractor to ensure they are as strong as possible. Dr. Nakamura agreed and noted the protocol and statistical analyses plan(s) should be preregistered.
- ***Extent of the review:*** An audience member questioned how applications could be judged without the applicant's track record. A more experienced investigator may write an application differently than one less experienced. Dr. Nakamura acknowledged that the anonymized reviews will not cover all five criteria.

CSR Diversity

Dr. Nakamura provided data on diversity within the total CSR workforce, with a focus on the SRO workforce, based on race and ethnicity, and on sex. He also showed similar data on membership and leadership of standing review committees.

Chairpersons and Standing Members by Race/Ethnicity and Sex in FY 2016

Race/ Ethnicity/Sex	% of Chairpersons	% of Standing Members
Female	37.0%	39.0%
White (Not Hispanic)	76.0%	66.0%
Asian (Not Hispanic)	11.0%	20.0%
URM	10.0%	12.0%

Workload

Application numbers continue to rise. The May 2016 Council rounds received a record number at more than 20,000. There is uneven distribution throughout the year. The effects of a growing application workload include pressure on the success rate, reviewer pressure, and more costs and needs for staff. Every increase of 1,000 applications results in an increase of \$1 million in associated reviewer and administrative costs.

The Scientific Management Review Board has suggested continuous submission, as the National Science Foundation has done. He shared slides from an experiment to eliminate deadlines by the NSF Surface Earth Processes Section. Applications showed an overall decline and were submitted more evenly across the course of the year, rather than in peaks. NSF staff said they believe without a time constraint, investigators submit better applications, but this is based on impressions, not evidence.

Archival e-Print Servers

Dr. Nakamura noted applicants can refer to articles not yet peer-reviewed, if they are readily accessible through an archival source. He asked for CSRAC feedback.

Discussion Highlights

- ***Continuous submission:*** Dr. Sano asked how continuous submission would affect the review cycle and budget. Dr. Nakamura said NIH's well-known budget cycle and deadlines would have to be taken into account. Discussion is underway for an experiment within one portfolio. Dr. Hollingsworth noted given the ebbs and flows in funding, many ICs make funding decisions in the summer. Dr. Nakamura said CSR has tried to track the time between review and funding. He said continuous submission may reduce workload, increase success rate, and speed up when applicants receive their awards.
- ***Resubmission:*** Dr. Hollingsworth asked about the impact of continuous submission on those who want to resubmit within the same fiscal year.
- ***Reviewer burden:*** Dr. Sano said the crux of the issue related to publications on preprint servers is the effect on reviewer burden. Dr. Nakamura said IC directors have endorsed the concept, given the speed of scientific communication, but it does mean reviewers have to look at the original literature.
- ***Purpose of preprint publications:*** Dr. Hollingsworth praised the idea when there is a new finding, noting it would be considered unvetted, similar to unpublished data at a meeting. He and Dr. Orr wondered if some investigators would use it as a strategy to bypass page limits. Dr. Targan also questioned if the addition would affect younger investigators. Dr. Essock noted this is inevitable, as biosketches include publication history. Dr. Nakamura said he will get feedback from SROs about how it is used.

VIII. Closing Comments

Dr. Nakamura thanked the CSRAC members rotating off the council for their service: Dr. Brinton, Dr. Essock, Dr. Hollingsworth, and Dr. Orr. He thanked all of CSRAC and acknowledged the dedicated work of CSR staff.

We do hereby certify that, to the best of our knowledge, the foregoing minutes of the September 26, 2016, meeting of CSRAC are accurate and complete. The minutes will be considered at the next meeting of the Advisory Council, and any corrections or comments will be made at that time.

Rene Etcheberrigaray, M.D.
Executive Secretary
Center for Scientific Review Advisory Council

Richard Nakamura, Ph.D.
Chair
Center for Scientific Review Advisory Council